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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,444	08/04/2006	David Rekosh	00958-06	9572

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UNIVERSITY OF VIRGINIA PATENT FOUNDATION
250 WEST MAIN STREET, SUITE 300
CHARLOTTESVILLE, VA 22902

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
06/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,444	REKOSH ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-37* is/are rejected.

7)☒ Claim(s) *38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 30 March 2010.

Claims 1-34 have been cancelled.

Claims 35-38 have been added and are currently examined.

Claim Objections

(Prior Objection – Withdrawn) The objection to claims 14-19 and 25-34 is withdrawn in light of the cancellation of the claims.

(New Objection – Necessitated by Amendment) New claim 38 is objected to for depending from a rejected base claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WITHDRAWN REJECTIONS

(Prior Rejection—Withdrawn) The rejection of claims 14, 16-18 and 27 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to the Applicants' amendment cancelling the claims.

(Prior Rejection—Withdrawn) The rejection of claims 11 and 12 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in response to Applicants' amendment.

NEW REJECTION – Scope of Enablement

(New Rejection – Necessitated by the Amendment) New claims 35-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting HIV replication in a cell by contacting the cell with a compound with a high toxicity index, *i.e.* compound 103833 and derivatives 311, 312, 314, 315, 318, 320, 321, 323-330, and 334-339, does not reasonably provide enablement for a compound with a low toxicity index, i.e. derivates 313, 316, 317, 319, 322 and 331-333. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragraph, the courts have put forth a series of factors (MPEP §2164.01(a)). See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the

claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Nature of the invention. Claims 35-37 are directed to a method of inhibiting HIV replication in a cell comprising contacting the cell with a compound.

Breadth of the claims. The breadth of the claimed invention in claims 35-37 encompasses inhibition of any strain or subtype of HIV using compound 103833 and its 29 analogs.

Working examples. The disclosure fails to provide any working embodiments that meet all of claimed limitations of HIV inhibition in cells. While there are cell assay examples of compounds including the one recited in the instant claims (spec. p. 34-46), these eight compounds and their respective analogs do not show consistent and uniform anti-HIV activity in different cell assays, as indicated by the inhibition concentrations (IC50) and the therapeutic indexes (TI) for the Rev assay in luciferase reporter HeLa cell line (p.36, Table 4), the viral assay in fresh human peripheral blood mononuclear cells (p. 40, Table 5), and the reverse transcriptase assay in U1 cell culture (p. 42-46, Table 6 and 8). Importantly, among the twenty-nine analogs of compound 103833, at least eight of them (analog no. 313, 316, 317, 319, 322 and 331-333) have IC50 concentration so close to the TC50 concentration, indicating that these eight analogs would kill the cells either before or while they get to inhibit HIV replication.

Guidance in the specification. The disclosure in the specification is limited to a number of lead compounds and their analogs that have been demonstrated to retain the desired inhibitory activity of HIV replication in a cell. The disclosure does not provide

clear-cut evidence that correlates any structural characteristics with the inhibition activity against all isolates of macrophage- and T-cell-tropic HIV, specifically blocking Rev function. Especially for the recited compound 103833, the 29 analogs show a wide range of toxicity index (TI) from 0.30 to 316. Therefore, based on the experimental evidence presented in the specification, any little change in the functional groups modifying the lead compound structure clearly contributes to a pronounced change in the potency of the inhibitor compound, which shows a high level of unpredictability in the HIV-inhibition function of any derivative or analog. Furthermore, the specification is remiss of other experimental evidence like T cell count and viral load measurement of cells before and after infection with different HIV strains. Most importantly, the experimental data disclosed in the specification shows that at least eight of the analogs of compound 103833 with IC50 concentration so similar to TC50 concentration that they kill the HIV-infected cell after contacting in addition to inhibit the HIV replication.

State of the prior art and predictability of the art. It is widely known in the art that high toxicity for a drug with *in vitro* HIV inhibitory activities precludes determination of *in vivo* anti-HIV activities (Olszewski *et al.*, 2004). In vitro cell assays are mainly for identifying potential HIV inhibitors from a library of analogs, which are not all effective inhibitors (Olszewski *et al.*, 2004). Thus, one skilled in the art would not assume all analogs derived from a base structure of an inhibitor compound would be equally effective.

Amount of experimentation necessary. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v.

Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case, there is insufficient evidence to demonstrate that those in the art would be able to use the claimed compound 103833 and all 29 analogs thereof to inhibit HIV replication in a cell. The specification provides experimental evidence showing that at least eight of the analogs have IC50 concentrations above 5 μM with high level of toxicity. The prior art shows that only a select few of analogs derived from the same base compound would exhibit the expected HIV inhibitory activity. Therefore, it would require undue and unpredictable experimentation for one skilled in the art to use the full scope of the claimed method.

Response to Arguments

Applicant's arguments filed 30 March 2010 have been fully considered but they are not persuasive. Applicants argued that new claims 35-38 recite a method of inhibiting HIV replication using compound 103833 and analogs thereof, all of which are disclosed in the specification. Applicants also argued that many of those disclosed in the specification have excellent HIV inhibition and Rev inhibiting activity.

Examiner appreciates Applicant's clarification of the data regarding the IC50 and TC50 presented in Table 8 of Example 5 on page 43-44 of the specification. Examiner agrees that the working examples demonstrate the inhibition activity of HIV replication and Rev function of selected compounds and their analogs in cells. As set forth above, the rationale of the enablement rejection and the Wands factor analysis have been modified accordingly to address the limitations in the new claims. Nonetheless,

applicants' response does not overcome the scope of enablement issue for the eight analogs (no. 313, 316, 317, 319, 322 and 331-333) that kill the cells at the same time as inhibit the HIV replication less effectively, when compared to the compound 103833.

Conclusion

Applicant's amendment necessitated the new ground of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas, can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Zachariah Lucas/
Primary Examiner, Art Unit 1648